HIV With Transmitted Drug Resistance Is Durably Suppressed by B/F/TAF at Week 144

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Introduction

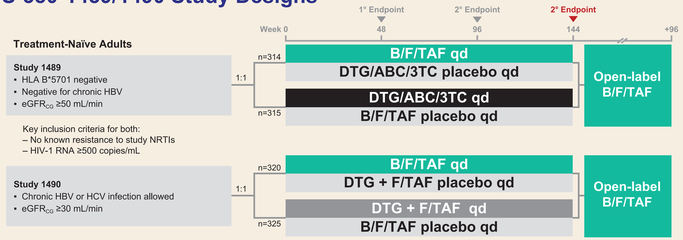
- The single-tablet regimen bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is a guidelines-recommended regimen with demonstrated safety, efficacy, and a high barrier to resistance[1-5]
- Studies 1489 (NCT02607930) and 1490 (NCT02607956) are two Phase 3 studies of B/F/TAF compared with dolutegravir (DTG)–containing regimens in treatment-naïve adults
  - B/F/TAF was noninferior to DTG/abacavir/lamivudine (DTG/ABC/3TC) and DTG + F/TAF through 144 wk of treatment[6]
  - Ongoing open-label extensions are evaluating continuing or switching to B/F/TAF through an additional 96 wk since completion of the blinded phase[7]
- Transmitted drug resistance (TDR) results from infection with an HIV-1 strain containing resistance-associated substitutions
  - TDR has been associated with an increased risk of suboptimal virologic response, virologic failure, and resistance development[8-11]
  - Both TDR by antiretroviral class (nucleos(t)ide reverse transcriptase [RT] inhibitor [NRTI], nonnucleoside RT inhibitor [NNRTI], protease [PR] inhibitor [PI], and integrase [IN] strand transfer inhibitor [INSTI]) and resistance to study drug regimen components (BIC, FTC, TAF, DTG, ABC, and 3TC) are important to consider

Objectives

- To assess the effect of preexisting drug resistance mutations on treatment outcomes using B/F/TAF, DTG/ABC/3TC, and DTG + F/TAF
- To evaluate virologic failure and emergent resistance in both studies

Methods

GS-US-380-1489/1490 Study Designs



eGFR$_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault equation; HBV, hepatitis B virus; HCV, hepatitis C virus; HLA, human leukocyte antigen.

- Population sequencing of HIV-1 PR and RT (Monogram Biosciences, South San Francisco, CA) was performed at screening
  - Resistance to study NRTIs was excluded (to FTC or TAF for both studies, and also to ABC or 3TC for Study 1489)
- Retrospective baseline next-generation sequencing of PR, RT, and IN (SEQ-IT GmbH & Co.KG, Kaiserslautern, Germany) was analyzed at a ≥15% cutoff, and results were combined with population sequencing results for the baseline resistance analysis
- Treatment outcomes were assessed at Week 144 using last on-treatment observation carried forward (LOCF)
- Resistance analyses were performed on participants with confirmed viral rebound of HIV-1 RNA ≥200 copies/mL through Week 144 or last visit who did not resuppress to <50 copies/mL while on study drug

Results

Study Population

- Of 1421 people with HIV screened for both studies, only 3 (<1%) were excluded due to TDR
  - 1 with M184V in RT, 1 with M184M/V in RT, and 1 with M184V, M41L, L210W, T215F/Y, and K219Q in RT
- Baseline characteristics of the pooled B/F/TAF group (n=634) were: median age 32 y, 89% men, 33% Black or African descent, 24% Latinx ethnicity, median HIV-1 RNA 4.42 $\log_{10}$ copies/mL, median CD4 cell count 442 cells/μL, and 90% asymptomatic HIV infection
  - Baseline characteristics were similar in the DTG/ABC/3TC and DTG + F/TAF groups

Preexisting NRTI- and INSTI-Associated Substitutions

Participants With Resistance Substitutions at Baseline, n (%)*	B/F/TAF n=634	DTG/ABC/3TC n=315	DTG + F/TAF n=325
Primary NRTI-associated†	21 (3)	8 (3)	6 (2)
1–2 TAMs	19 (3)	6 (2)	6 (2)
M41L	4 (<1)	2 (<1)	1 (<1)
K65E/R‡	2 (<1)	1 (<1)	0
D67N	3 (<1)	2 (<1)	1 (<1)
K70R	3 (<1)	0	1 (<1)
L74V	1 (<1)	0	0
Y115F	0	1 (<1)	0
L210W	0	0	1 (<1)
K219E/N/Q/R	11 (2)	3 (1)	2 (<1)
Primary INSTI-associated§	7 (1)	4 (1)	6 (2)
T97A	6 (<1)	4 (1)	6 (2)
Q148H	1 (<1)	0	0
Secondary INSTI-associated§	326 (52)	152 (48)	161 (50)
M50I	126 (20)	48 (15)	62 (19)
H51Y	0	1 (<1)	1 (<1)
L68I/V	4 (<1)	2 (<1)	2 (<1)
V72T	3 (<1)‖	1 (<1)	3 (<1)
L74M	1 (<1)	5 (2)	2 (<1)
Q95K	1 (<1)	0	0
S119P/R/T	197 (31)	103 (33)	101 (31)
A128T	3 (<1)	0	0
E138A/K	1 (<1)	2 (<1)	2 (<1)
G140S	1 (<1)	0	0
Q146R	1 (<1)	0	0
S153A	3 (<1)	1 (<1)	2 (<1)
E157K/Q	35 (6)	12 (4)	12 (4)
G163K/R	6 (<1)	5 (2)	6 (2)

*Primary NRTI-resistance (R) substitutions: M41L, K65E/N/R, D67N, T69 insertions, K70E/R, L74I/V, Y115F, Q151M, M184I/V, L210W, T215F/Y, and K219E/N/Q/R in RT; primary INSTI-R substitutions: T66A/I/K, E92G/Q, T97A, F121Y, Y143C/H/R, S147G, Q148H/K/R, N155H/S, and R263K in IN; secondary INSTI-R substitutions: M50I, H51Y, L68I/V, V72A/N/T, L74M, Q95K/R, G118R, S119P/R/T, F121C, A128T, E138A/K, G140A/C/S, P145S, Q146I/K/L/P/R, V151A/L, S153A/F/Y, E157K/Q, G163K/R, and E170A in IN; †Denominators for PR and RT gene analyses: 634 B/F/TAF, 315 DTG/ABC/3TC, and 325 DTG + F/TAF; population sequencing data were available for all these participants; deep sequencing data were available for 632 B/F/TAF, 314 DTG/ABC/3TC, and 324 DTG + F/TAF participants; ‡K65E/R mutation was not detected in any participants at screening by population genotype; K65E/R mutations listed here were detected retrospectively by deep sequencing; §Denominators for IN gene analyses: 632 B/F/TAF, 314 DTG/ABC/3TC, and 324 DTG + F/TAF; population sequencing data were available for 21 B/F/TAF, 12 DTG/ABC/3TC, and 14 DTG + F/TAF participants; deep sequencing data were available for all these participants; ‖1 participant had V72T at Day 1 at 2.83% and was included in this analysis. TAMs, thymidine analog mutations.

- Primary NRTI- and INSTI-associated substitutions were infrequent in this treatment-naïve population

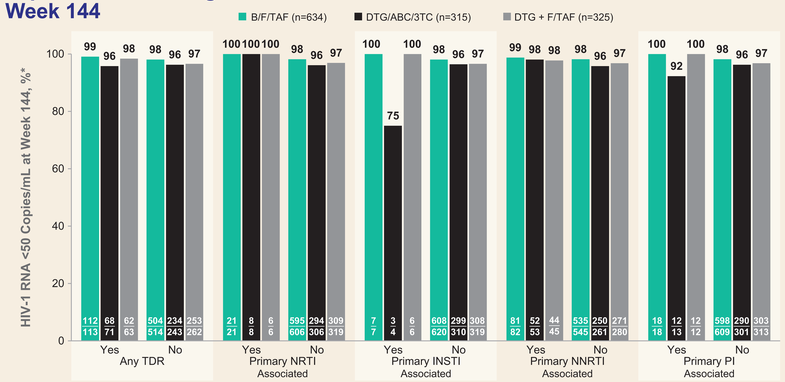
Preexisting NNRTI- and PI-Associated Substitutions

Participants With Resistance Substitutions at Baseline, n (%)*	B/F/TAF n=634	DTG/ABC/3TC n=315	DTG + F/TAF n=325
Primary NNRTI-associated†	82 (13)	53 (17)	45 (14)
L100I	3 (<1)	0	0
K101E/P	5 (<1)	2 (<1)	0
K103N/S	42 (7)	27 (9)	23 (7)
V106A	0	1 (<1)	2 (<1)
V108I	1 (<1)	4 (1)	2 (<1)
E138A/G/K/Q	28 (4)	17 (5)	14 (4)
V179L	0	0	1 (<1)
Y181C	3 (<1)	2 (<1)	2 (<1)
Y188C/L	2 (<1)	2 (<1)	1 (<1)
G190A/E/Q/S	5 (<1)	2 (<1)	3 (<1)
H221Y	1 (<1)	1 (<1)	0
P225H	3 (<1)	1 (<1)	1 (<1)
M230I	1 (<1)	0	0
Primary PI-associated†	19 (3)	13 (4)	12 (4)
D30N	2 (<1)	2 (<1)	0
V32I	1 (<1)	0	1 (<1)
M46I/L	7 (1)	3 (1)	6 (2)
I47V	1 (<1)	1 (<1)	0
I50L/V	1 (<1)	0	1 (<1)
Q58E	3 (<1)	5 (2)	3 (<1)
L76V	0	0	1 (<1)
V82A/L	4 (<1)	0	0
I84V	0	0	1 (<1)
L90M	3 (<1)	2 (<1)	4 (1)

*Primary NNRTI-R substitutions: L100I, K101E/P, K103N/S, V106A/M, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, and M230I/L in RT; primary PI-R substitutions: D30N, V32I, M46I/L, I47A/V, G48V, I50L/V, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, and L90M in PR; †Denominators for PR and RT gene analyses: 634 B/F/TAF, 315 DTG/ABC/3TC, and 325 DTG + F/TAF; population sequencing data were available for all these participants; deep sequencing data were available for 632 B/F/TAF, 314 DTG/ABC/3TC, and 324 DTG + F/TAF participants.

- Primary NNRTI-R was frequent at 13% for B/F/TAF
- Primary NNRTI-R and PI-R substitutions may be markers for low-level or archived primary NRTI-R substitutions[12]

Impact of Preexisting Resistance Substitutions on Treatment Outcome at Week 144



Key Resistance Substitutions at Baseline	HIV-1 RNA <50 Copies/mL at Week 144, n/N (%)* B/F/TAF n=634	DTG/ABC/3TC n=315	DTG + F/TAF n=325
Primary NRTI-associated			
1–2 TAMs	19/19 (100)	6/6 (100)	6/6 (100)
K65E/R	2/2 (100)	1/1 (100)	0
Primary INSTI-associated			
Q148H	1/1 (100)	0	0
Primary NNRTI-associated			
K103N/S	42/42 (100)	27/27 (100)	22/23 (96)
E138A/G/K/Q	27/28 (96)	17/17 (100)	14/14 (100)

*LOCF outcome analysis did not include 7 B/F/TAF and 1 DTG/ABC/3TC participant who had no on-treatment postbaseline HIV-1 RNA data; 1 of these B/F/TAF participants had a primary PI-associated resistance substitution.

- >99% of B/F/TAF participants with preexisting resistance substitutions had virologic suppression at Week 144 or last visit

Virologic Resistance Results at Week 144

Participants, n (%)	B/F/TAF n=634	DTG/ABC/3TC n=315	DTG + F/TAF n=325
Met criteria for resistance testing*	8 (1)	6 (2)	7 (2)
NRTI-R detected	0	0	0
INSTI-R detected	0	0	0

*Resistance testing performed for participants with confirmed HIV-1 RNA ≥200 copies/mL or ≥200 copies/mL at last visit, with no resuppression of HIV-1 RNA to <50 copies/mL while on study drug.

- No resistance to any components of the treatment regimens occurred in any treatment group
- In these studies, participants could remain on study drug if they had virologic failure without resistance
  - 2/8 B/F/TAF, 6/6 DTG/ABC/3TC, and 4/7 DTG + F/TAF participants had multiple confirmed virologic rebounds during the studies, and none developed drug resistance

Conclusions

- Overall, treatment with B/F/TAF, DTG/ABC/3TC, or DTG + F/TAF led to high rates of durable virologic suppression in HIV-1 treatment-naïve participants
- The presence of transmitted, preexisting resistance substitutions did not affect treatment outcomes in these clinical trial settings
  - For B/F/TAF participants with NRTI-, NNRTI-, or PI-R substitutions, high treatment efficacy was seen at Week 144 or last visit
  - For B/F/TAF participants with study drug resistance to BIC or TAF (1 with Q148H+G140S in IN and 2 with K65E in RT), high efficacy was also seen; however, use of B/F/TAF is not generally recommended in these cases
- No participant had treatment-emergent resistance to study drugs detected through Week 144
- B/F/TAF has broad clinical utility as an initial or switch regimen,[12] including in people with HIV-1 with or without resistance substitutions

References: 1. Biktarvy [EPAR]. Foster City, CA: Gilead Sciences, Inc., 6/18; **2.** Biktarvy [package insert]. Foster City, CA: Gilead Sciences, Inc., 6/19; **3.** Dept of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV, 12/19; **4.** EACS European AIDS Clinical Society Guidelines Version 10.0, 11/19; **5.** Saag MS, et al. JAMA 2020;324:1651-69; **6.** Orkin C, et al. Lancet HIV 2020;7:e389-e400; **7.** Workowski K, et al. CROI 2021, abstr 2268; **8.** Little SJ, et al. N Engl J Med 2002;347:385-94; **9.** Mbunkah HA, et al. J Infect Dis 2020;221:1584-97; **10.** Paredes R, et al. J Infect Dis 2010;201:662-71; **11.** Pillay D, et al. AIDS 2006;20:21-8; **12.** Andreatta K, et al. HIV Glasgow 2020, P123.

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